REMARKS

Reconsideration and withdrawal of the rejections of the application is respectfully requested in view of the above amendments and the following remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS

Claims 1-56 are pending in this application, of which Claims 29, 30, 32-41, and 45-56 have been withdrawn from consideration without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. No new matter has been added..

It is submitted that the Claims 1-28, 31, and 42-44 herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims are in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. FORMAL MATTERS

The oath or declaration was found to be defective. Applicants herewith submit a new oath/declaration in compliance with 37 C.F.R. § 1.67(a). The date of filing of U.S. patent application Serial No. 10/059,521 has been corrected to read January 29, 2002, and the date of filing of the U.S. provisional application Serial No. 60/264,796 is corrected to read January 29, 2001.

III. THE REJECTIONS UNDER 35 U.S.C. $112 ARE OVERCOME

Claims 20-24 and 42-44 were rejected under 35 U.S.C. §112 (second paragraph) as allegedly being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20, in step (a) thereof, was regarded by the Examiner as vague and indefinite because it was unclear "how a "cell surface marker indicator" is capable of selectively binding a cell surface marker."

Claim 20, and the Claims 23 and 24 dependent therefrom, is herein amended accordingly to address the Examiner's concerns.

Claim 42 was rejected as vague and indefinite because it was unclear as recited what proliferative status of the primitive hematopoietic cells is suitable for transplantation and how it is identified.

Claim 42 is herein amended to more clearly indicate that the positive proliferative status of cells identifies cells suitable for transplantation.

Claim 43 was rejected as having improper antecedant basis in reciting "a population of primitive hematopoietic cells."

Claim 43 has been amended to read "the population of hematopoietic cells."

Claim 44 was rejected as vague and indefinite because it was unclear as recited how the at least one test compound is identified.

Claim 44 has been amended to more clearly indicate that the proliferative status of a target cell population in contact with a test compound is compared to the proliferative status of a cell population not in contact with the test compound, and that a change in the proliferative status of the target population relative to that of the non-contacted population indicates the ability of the test compound to modify the target cell proliferative status.

The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

Reconsideration and withdrawal of the Section 112 rejections are earnestly requested.

IV. THE REJECTIONS UNDER 35 U.S.C. §103 ARE OVERCOME

Claims 1-28, 31, and 42-44 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over *Crouch et al.*, ((1993) J. Immunol. Meth. 160: 81-88) in view of *Bell et al.*, (US 2002/0120098 Al). These rejections are addressed collectively and are respectfully traversed.

It is impossible to combine, as contended by the Office Action, elements from the hemoglobin-based cell proliferation based system of *Bell et al.* with those from the luciferase-based assay of *Crouch et al.* to provide the functional assay method of the present invention. There is no combination of *Bell et al.* and *Crouch et al.* that could not provide a functional assay, as taught and claimed in the present application, in light of prior art teachings and the inventor's own data.

Claim 1 is herein amended to more clearly define the primitive hematopoietic cells. Support for the amendment is found in Example 1 and 2 of the specification as filed and therefore does not constitute new matter. The present application teaches and claims methods for rapidly determining the proliferative status of a population of primitive hematopoietic cells, the method comprising the steps of incubating a cell population comprising primitive hematopoietic cells substantially free of hemoglobin in a cell growth medium comprising fetal bovine serum having a concentration of between 0% and 30% and methyl cellulose having a concentration of between about 0.4% and about 0.7%, and in an atmosphere having between about 3.5% oxygen and 7.5% oxygen, contacting the cell population with a reagent capable of generating luminescence in the presence of ATP, and detecting luminescence generated by the reagent contacting the cell population, the level of luminescence indicating the amount of ATP in the cell population, wherein the amount of ATP indicates the proliferative status of the primitive hematopoietic cells.

The Office Action dated January 25, 2005 states:

> *Crouch et al.* differ from the instant invention in failing to disclose that the cell growth culture medium includes methyl cellulose having a

concentration of about 0.4% to 0.7% methyl cellulose and maintained in an atmosphere having between about 3.5% to 7.5% oxygen. *Crouch et al.* further differ from the instant invention in failing to disclose generating a hematopoietic population enriched in progenitor cells and stem cells from animal tissue such as bone marrow, fetal liver, and spleen, isolated from cow, sheep, pig, horse, goat, dog, cat, and primates, and determining their suitability for transplantation. *Crouch et al.* also does not teach isolating and identifying specific subpopulations of primitive hematopoietic cells using cell surface markers. Lastly, *Crouch et al.* does not teach contacting the primitive hematopoietic cells with a test compound and determining its ability to modulate proliferation of the cells.

With respect to the document of *Bell et al.*, the Office Action states that:

Bell et al. disclose methods for enhancing stimulation of hematopoiesis (erythropoiesis) using hemoglobin. Hematopoiesis involves the proliferation of hematopoietic stem cells and hematopoietic progenitor cells and the stimulation is specific for hematopoietic colony-forming cell erythroid macrophage, megakaryocyte stem cells (CFC-GEMM) (see page 4, column 1, [0026], page 7, column 2, [0071], and page 9, column 2, [0085]). According to *Bell et al.*, the burst forming unit-erythroid (BFU-E) represents the most primitive hematopoietic or erythroid progenitor and forms large multi-clustered hemoglobinized colonies (see page 1, column 1, [0004]). In practice, *Bell et al.* teach incubating primitive hematopoietic cells in a cell growth medium comprising 30% fetal bovine serum, about 0.4% to about 0.7% (0,8%) methyl cellulose which increases viscosity in culture media, and in an atmosphere having between about 3.5% to 7.5% (5%) oxygen. *Bell et al.* also teach contacting the sample with cytokine such as GM-CSF and Flts ligand to generate a cell population substantially enriched in CFC-GEMM stem cells for use in cell proliferation assay (see page 7, column 2, [0071], page 9, column 2, [0084-0092], and Examples 1 and 2). *Bell et al.* disclose that erythroid progenitor colony formation is enhanced at lower, more physiological oxygen tensions, such as 5% oxygen (see page 11, column 1, [0098-0101]. These enriched hematopoietic stem cells or progenitor cells can be obtained from bone marrow, cord blood, or peripheral blood, and if determined to have adequate proliferate status, can be transplanted into a recipient patient (see page 4, column 2, [0030] and page 7, column 2, [0078]). Hematopoietic stem cells or progenitor cells can also be obtained and enriched from animal tissue such as bone marrow, cord blood, fetal liver, or spleen, of dog, cow, horse, cat, pig, sheep, goat, chicken, primate, or human (see page 8, column 2, [0076-0078]). *Bell et al.* further teach that subpopulations of primitive hematopoietic cells are characterized by the presence of specific hematopoietic progenitor cell surface markers such as CD34 and

> glycophorin A (see page 12, column 1, [0105]). These subpopulations can be selectively isolated by binding the cells with antibodies specific for their cell surface markers such as anti-CD34 and anti-glycophorin A or by magnetic bead separation (STEMSEP™ system) and selectively determined by flow cytometry or flow activated cell sorting (see page 17, column 1, [0044 and 0045] and Example 9). *Bell et al.* further teach contacting primitive hematopoietic cells having a target cell population with a test a compound (Ganciclovir) and determining its ability to modulate, i.e. inhibit, proliferation or differentiation of the target cell population. Result of the testing is compared with negative control (see Example 11).

The methods as taught by *Bell et al.* incorporate hemoglobin or stabilized variants of hemoglobin as an essential component of the cell culturing systems to promote the growth of erythropoietic cells. *Bell et al.* also teaches only the stimulation of erythropoietic cell proliferation. Indeed, *Bell et al.* teaches that hemoglobin *alone* or *in conjunction with* cytokines such as Il-3 or EPO. *Bell et al.*, therefore, does not teach the method of the present application for rapidly determining the proliferative status of any hematopoietic cell-types, including non-erythropoietic cells, as claimed in the present application.

It is also stated in the Office Action of January 25, 2005, that:

> [I]t would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Bell in using a culture growth medium having 30% fetal bovine serum, 0,8% methyl cellulose, and in an atmosphere having between about 5% oxygen into the proliferation assay taught by Crouch because Bell specifically taught that hematopoietic progenitor cells or stem cells favor survival and growth in a medium having such a composition for use in proliferation assays.

It is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985) and that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. It is further respectfully submitted that there is no teaching or suggestion in the cited art to motivate one of

ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

Colin et al., ((2000) Gene Therapy 7: 1333-1336), a copy of which is submitted herewith as Exhibit A, teaches that the inclusion of heme-containing molecules in a luciferase-based ATP assay system significantly impairs the detection of the luminescence due to adsorption of emitted light by the heme moiety. According to *Colin et al.*, the reduction in the measured level of light is because heme has peaks of absorbance corresponding to the wavelengths of the light generated by luciferases. The reduction or loss of measurable emitted light occurs regardless of the environment of the heme and luciferase (*Colin et al.* in Fig. 4, which shows the coincidence of the luciferase emission spectrum with the absorbance spectra of heme alone, or with homogenized tissue mixes).

Heme interference also occurs in the tissue-free in vitro environment of the methods of the present application. Accompanying this response is a Declaration under 37 C.F.R. § 1.132 by Dr. Ivan N. Rich, who is the inventor of the present application.

The Declaration, at paragraphs 4(a)-4(l), provides experimental results that clearly show that heme, in the form of free hemoglobin, in the luciferase-based assays according to the methods of the present application prevents the measurement of nucleated cell proliferation by suppressing detectable luciferase-generated luminescence, in accordance with the data of *Colin et al.*

The Declaration, at paragraphs 5(a)-5(f), also provides experimental results showing that with whole blood, it is erythrocytes that stimulate luminescence and lead to false positive results. The observed stimulation was due to elevation of the oxygen content of the luciferase assay system, thereby promoting the reaction that produces luminescence.

Therefore, it would have been impossible to combine, as contended by the Office Action, the hemoglobin-based cell proliferation based system of *Bell et al.* with the luciferase-based assay of *Crouch et al.* to provide the functional assay method of the present invention.

The Office Action failed to indicate any source of motivation for combining the hemoglobin-containing systems for promoting the growth of erythropoietic cells as taught by *Bell et al.*, with the teachings of *Crouch et al.* to produce the functional luciferase-based ATP assay as claimed in the present application.

Attention is drawn to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." For the §103 rejection to be proper, both the suggestion of the claimed invention and the *expectation of success* must be founded in the prior art, and not Applicant's disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Accordingly, it is respectfully submitted that when one considers all of the teachings in the art, and the mandates of the case law and the MPEP, it is clear that the rejections cannot stand. The cited documents fail to teach or suggest the instant invention, or provide any motivation for their combination. *Colin et al.*, and the inventor's own data as submitted herein, clearly demonstrate that the combination of teachings proposed by the Office Action cannot provide a function assay as taught and claimed in the present application. Accordingly, in view of the herein arguments, amendments to the claims, the accompanying Exhibit A and the Declaration submitted herewith, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt

issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.. The Commissioner is hereby authorized to charge any additionally required fee, or credit any overpayment in fees, to Deposit Account No. 50-0320.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: _____

David J. Hayzer J.D., Ph.D.
Reg. No. 43,329
Telephone: (212) 588-0800
Facsimile: (212) 588-0500